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Natural History of Metastatic Renal Cell Carcinoma in Patients Who Underwent Consultation for Allogeneic Hematopoietic Stem Cell Transplantation

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ABSTRACT

We characterized the natural history of metastatic renal cell carcinoma (RCC) and identified prognostic factors among patients who did or did not undergo allogeneic hematopoietic stem cell transplantation (HSCT). A total of 99 patients (23 who underwent HSCT and 76 who did not) were included in the study. Overall survival rates were comparable between the HSCT and no-HSCT groups (excluding patients with poor performance status or brain metastasis from the latter group) at a median 17.4 months of follow-up (P = .92). In univariate analyses, Fuhrman's nuclear grade 4 (P = .05), high serum calcium (P = .002), or low hemoglobin levels (P = .02), 3 or more metastatic sites (P = .02), and <12 months from diagnosis to initial recurrence (P = .04) were identified as poor prognostic factors. In multivariate analyses, 3 or more metastatic sites (P = .005) and low hemoglobin levels (P = .02) were poor prognostic factors. In the HSCT group, median survival times from consultation and from transplant were 25 and 19 months for those with 0 prognostic factors (n = 7) and 11 and 7 months for those with 1 or more prognostic factors (n = 16). In conclusion, previous concerns that HSCT would negatively affect long-term outcome of patients with metastatic RCC were not confirmed. Patients with any of these poor prognostic factors should not consider HSCT for metastatic RCC. The role of allogeneic HSCT for patients with no prognostic factors should be explored in clinical trials for patients with targeted therapy-resistant metastatic RCC.

KEY WORDS

Allogeneic stem cell transplantation • Renal cell carcinoma • Overall survival • Prognostic factors

INTRODUCTION

Metastatic renal cell carcinoma (RCC) carries an extremely poor prognosis, with 5-year survival rates of <10% [1]. Chemotherapy for metastatic RCC produces response rates of only about 15% to 30%, without durable complete responses and little impact on survival [2]. Although cytokine therapy (eg, interleukin [IL]-2, interferon) is thought to be superior to conventional cytotoxic chemotherapy for metastatic RCC, response rates are still poor at about 15% to 20% [3-6].

Recent advances in understanding the molecular genetics of RCC have opened the way for the concept of molecular-targeted therapy. Of the new agents currently being investigated (eg, antiangiogenic drugs [7-14], raf-kinase inhibitors [15-19], and the mammalian target of rapamycin (mTOR) inhibitors [20-22]), some seem to have positive effects on survival of patients with metastatic RCC. Overall response rates to targeted therapy have ranged from 2% to 40% [23].

Allogeneic hematopoietic stem cell transplantation (HSCT) is a well-established treatment option for he-

matologic malignancies. Allogeneic HSCT can induce an immune-mediated graft-versus-tumor (GVT) effect [24], which has been best demonstrated against leukemias and lymphomas [25,26]. In 2000, Childs et al. [27] reported a clear GVT effect with allogeneic HSCT in patients with cytokine-refractory metastatic RCC. Since that time, we and others have reported clinical evidence of GVT effects in metastatic RCC, although those studies involved relatively small numbers of patients [28-35].

Allogeneic HSCT is associated with substantial risks of treatment-related morbidity and mortality (TRM), primarily related to graft-versus-host disease (GVHD) and infections. Many eligible patients hesitate to choose allogeneic HSCT because of its high TRM rates (reportedly 15%) [36]. In addition, a considerable proportion of patients referred to transplant clinics do not meet the eligibility criteria for transplant regardless of their preferences (eg, lack of an HLA-compatible donor or poor performance status [PS]). Therefore, assessing the efficacy of allogeneic HSCT and its role for RCC is complex. Patients receiving HSCT have been highly selected and cannot simply be compared with patients with metastatic RCC in other published studies.

In this study, we retrospectively characterized all patients who presented to the Stem Cell Transplantation Center at The University of Texas M.D. Anderson Cancer Center considering undergoing allogeneic HSCT for metastatic RCC, and we identified prognostic factors associated with prognosis among patients who did or did not undergo allogeneic HSCT. This is the first retrospective data set that dissects the natural history of metastatic RCC in patients who underwent consultation for allogeneic HSCT.

MATERIALS AND METHODS

Patients

Subjects were chosen from a total of 110 patients suspected of having metastatic RCC who were referred between September 1999 and November 2003 to the Stem Cell Transplantation Center at M.D. Anderson Cancer Center to consider allogeneic HSCT as a treatment option. Of these 110 patients, 11 were excluded from the analysis (Figure 1), 4 with coexisting malignancies (cervical cancer, malignant teratoma, or follicular lymphoma [1 of whom had received HSCT]), 1 with adenocarcinoma of gastrointestinal origin rather than RCC, 4 for lack of pathologic materials for confirmation, and 2 for having no sign of metastatic disease at the time of the consultation. This study was reviewed and approved by the institutional review board of M.D. Anderson.

The transplant group consisted of 23 patients, all of whom met our eligibility criteria [32]. Briefly, those criteria were age 70 years or younger, with histologic confirmation of metastatic disease, excluding pure sarcomatoid and pure transitional cell carcinoma types. Previous treatments were allowed. Response to prior therapy was not required. Other eligibility criteria for transplantation included having a related or unrelated

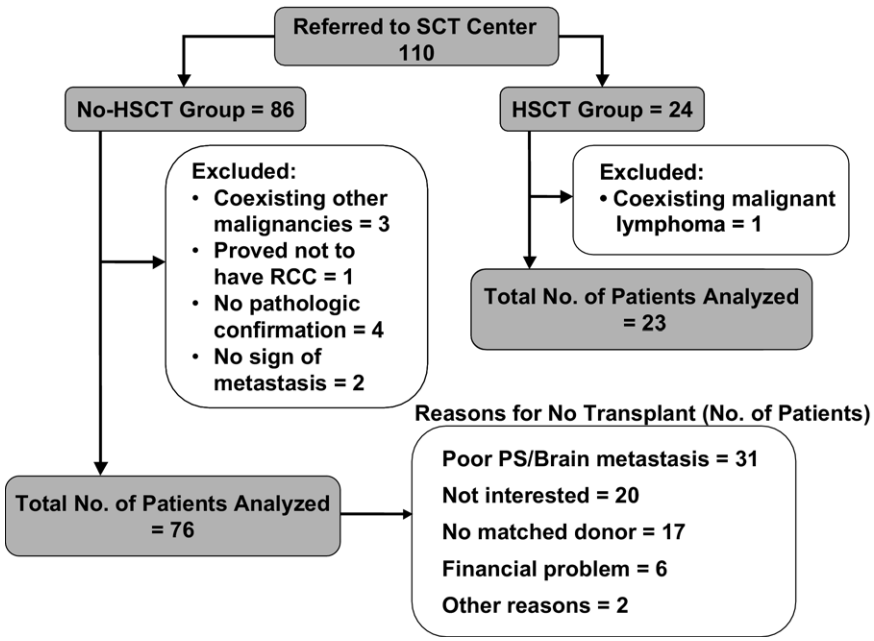

Figure 1. Derivation of sample sizes and reasons for not undergoing transplantation among the no-transplant group. Most of the comparisons made in this study were between the HSCT group (n = 23) and a subset of the no-HSCT group (n = 45) that excluded 31 patients with poor PS or brain metastases. HSCT, hematopoietic stem-cell transplantation; RCC, renal cell carcinoma.

HLA-compatible donor, good PS (a score of 0 or 1 on the Eastern Oncology Cooperative Group [ECOG] scale), and adequate organ function (defined as creatinine ≤ 2.0 mg/dL, total bilirubin ≤ 2.0 mg/dL, and left ventricular ejection fraction >50%). The preparative regimen for the transplant consisted of fludarabine (total dose 125 mg/m^2) and melphalan (140 mg/m^2). GVHD prophylaxis consisted of tacrolimus and mini-methotrexate (5 mg/m^2 intravenously on days 1, 3, and 6). Donor lymphocyte infusion (DLI) was given if there was no GVHD and no tumor response by 6 weeks after the transplant [32]. Response to therapy was evaluated at 3-month intervals. Evaluations included chest X-ray, skeletal scintigraphy, and chest and abdominal/pelvic computed tomography [32]. Disease response to transplant was classified as followed: complete response (CR) was the disappearance of all disease and symptoms related to the tumor for >4 weeks; partial response (PR), a >50% reduction in the sum of the products of the diameters of each measurable lesion measured on diagnostic images for >4 weeks; minor response (MR), a reduction in measurable lesions too small to qualify as a PR; stable disease (SD), no change in tumor size; and progressive disease (PD), the appearance of new lesions or a >25% increase in the sum of the products of diameters of any measurable lesions [32].

Data Collection

For patients who did not undergo transplantation, the reasons for not undergoing HSCT were grouped in 1 of 5 categories: poor PS or the presence of brain metastases; no interest; no available donor; financial difficulties; or other. If patients had not undertaken a search for a donor or for financial approval, in the absence of other major medical and social reasons, we assumed that those patients were not interested in HSCT. Follow-up was done by contacting the patients or their treating physicians.

Histologic slides were reviewed to confirm the diagnosis. Patients' status was updated through September 30, 2005.

Outcome Measures and Statistical Considerations

Data from all eligible patients were analyzed with descriptive statistics. Median overall survival (OS) time was estimated by the method of Kaplan and Meier. A Cox proportional hazards regression model was then used to test several factors for possible significance as predictors of OS.

RESULTS

Patient Characteristics

The median follow-up time for all 99 patients was 14.8 months (range: 0.2-65.6 months). After the consultation, 23 patients (23%) underwent HSCT and 76 patients (77%) did not (Figure 1). Patient characteristics are summarized in Table 1.

For the purposes of this study, further comparisons were made mostly between patient in the HSCT group and a subset of the no-HSCT group (those with good PS [ECOG score <2] and without brain metastases). Because patients with poor PS or brain metastases were considered ineligible for HSCT, including those patients in the analysis, it would have biased the results. No difference in PS was found between the HSCT group and the no-HSCT subgroup with good PS and no brain metastases (P = 1.00). However, the number of patients who had had IL-2 therapy and the number of treatment cycles received before consultation were less in the no-HSCT subgroup than in the HSCT group (P = .02 for both) (Table 1). Otherwise, the characteristics were similar between groups.

In terms of types of preconsultation treatments, the only difference found between the HSCT group and the entire no-HSCT group (n = 76) was a history of IL-2-based therapy; 63% of the HSCT group had received IL-2-based cytokine therapies before consultation, but only 37% of the no-HSCT subgroup had received such therapies (P = .03). Roughly 20% of the patients in both groups had received antiangiogenic therapies before consultation. Most of those therapies were thalidomide, but a few patients had received tyrosine-kinase inhibitors before consultation (4% of the no-HSCT group and 0% of the HSCT group).

The types of treatment given after the consultation were different in the HSCT group and in the no-HSCT group (Table 2). Forty patients in the no-HSCT group (53%) were given chemotherapy, but only 1 patient in the HSCT group (4%) was given chemotherapy after consultation, which was given as treatment after relapse (P < .001). Twenty-four patients in the no-HSCT group received thalidomide versus 0 in the HSCT group (P < .001). Patients in the no-HSCT group were also more likely to have received cytokine therapy (28 in no-HSCT versus 4 in HSCT [again, given as treatment after relapse]; P = .08) or tyrosine-kinase inhibitors (12 in no-HSCT versus 1 in HSCT, P = .09).

Reasons for Not Undergoing Allogeneic HSCT

The primary reasons for not undergoing allogeneic HSCT are shown in Figure 1. The most common reasons were poor PS or the presence of brain metastases (n = 31) and lack of interest on the part of the patient (n = 20). The median time between initial disease recurrence and subsequent consultation at M.D. Anderson tended to be longer for patients with poor PS or brain metastases than for the other subgroups (11.3 months versus 3.7 months for the no-interest group [P = .06], 3.5 months for the no-donor

Table 1. *Patient Characteristics*

Variable	HSCT (N = 23)	No-HSCT without Poor PS/BM (N = 45)	Poor PS/BM (N = 31)	*P* values* (Column 1 versus Column 2)
Sex				
Male	17	39	22	.32
Female	6	6	9	
Age: range (median)				
At diagnosis	28-62 (48)	25-69 (54)	25-68 (50)	
At consultation	30-63 (51)	25-69 (56)	31-69 (51)	
Median time (months) from diagnosis to consultation (range)	25.5 (2.8-151)	9.0 (0.2-100)	17.9 (24.3-112)	.09
Histology				
Clear cell	15	32	20	.07†
Papillary	4	3	8	
Sarcomatoid	0	4	0	
Granular	2	0	1	
Other	2	3	0	
Unknown	0	3	2	
Fuhrman's nuclear grade				
2	2	5	3	.55
3	12	22	14	
4	7	10	8	
Unknown	2	8	6	
Previous IL-2 therapy				
No	9	32	17	.02
Yes	14	13	14	
Previous IFN therapy				
No	8	26	8	.13
Yes	15	19	23	
Performance status at consultation				
0 or 1	22	44	13	1
≥2	1	1	18	
Previous Nephrectomy				
No	0	4	3	.29
Yes	23	41	28	
No. of Abnormal Laboratory Findings‡				
0	8	16	4	.92
1	11	18	10	
2	4	5	11	
3	0	1	3	
NA	0	5	3	

HSCT indicates hematopoietic stem cell transplantation; PS/BM, performance status/brain metastasis; IL-2, interleukin-2; IFN, interferon.
The following factors were evaluated and found to be no different between the two groups: history of cytokine-based therapy, number of chemotherapy regimens before cosultation, number of sites of metastatic disease.
*Fisher's exact test or Mantel-Haenszel chi-square test, comparing HSCT versus no-HSCT without poor performance status or brain metastases.
†*P* value for clear cell versus nonclear cell was 0.59.
‡Abnormal findings were hemoglobin level <13 g/dL for males or <11.5 g/dL for females; corrected serum calcium level of >10 g/dL; or lactate dehydrogenase levels >1.5 times the upper limit of normal.

group [*P* = .28], and 2.6 months for the financial-problem group [*P* = .15]).

Overall Response Rate

The overall response rate (CR + PR) in the HSCT group was 26%. In terms of the best responses, 4 patients (17%) achieved CR, 2 (9%) achieved PR, 5 (22%) achieved MR, and 5 (22%) experienced SD. Five other patients experienced PD, and 2 patients died of acute GVHD (aGVHD) before evaluation for disease response. A total of 17 patients in the HSCT group (74%) eventually died, at a median 7 months (range: 0.6-28.5 months) after HSCT, a median of 11 months (range: 3.2-37.1 months) after the initial consultation (Table 3). TRM rates were 17% at day 100 and 26% at 12 months after transplantation. The cumulative nonrelapse mortality rate was 39%.

Of the 6 patients alive at last follow-up after HSCT, 5 were alive with controlled disease (Table 4). One patient was alive in CR at 28.7 months after

Table 2. *Treatments After Consultation*

Therapies	No-HSCT group n = 76 n (%)	HSCT group n = 23 n (%)	*P* value
Chemotherapy	40 (52.6)	1 (4.2)	<.001
Fluorouracil	14 (18.4)	1 (4.2)	
Gemcitabine	27 (35.5)	0 (0.0)	<.001
Capecitabine	24 (31.6)	0 (0.0)	<.001
Cisplatin, Carboplatin	2 (2.6)	0 (0.0)	
Vinblastine	2 (2.6)	0 (0.0)	
Doxorubicin	3 (3.9)	0 (0.0)	
Ifosfamide	2 (2.6)	0 (0.0)	
Fludarabine	1 (1.3)	0 (0.0)	
Methotrexate	1 (1.3)	0 (0.0)	
Paclitaxel	1 (1.3)	0 (0.0)	
Cytokine-containing therapy	28 (36.8)	4 (16.7)	.08
IFN-based therapy	21 (27.6)	2 (8.3)	.06
IL-2-based therapy	15 (19.7)	3 (12.5)	
Targeted therapy (including anti-angiogenic therapy)	31 (40.8)	2 (8.3)	.005
Thalidomide	24 (31.6)	0 (0.0)	<.001
Bevacizumab	4 (5.3)	2 (8.3)	
Imatinib	2 (2.6)	0 (0.0)	
Sorafenib	4 (5.3)	0 (0.0)	
Erlotinib	3 (3.9)	1 (4.2)	
SU-5416	5 (6.6)	0 (0.0)	
CP-675,206	1 (1.3)	0 (0.0)	
ABT510	1 (1.3)	0 (0.0)	
Any tyrosine-kinase inhibitor	12 (15.8)	1 (4.2)	.09
Local therapy			
Palliative surgery	2 (2.6)	2 (8.3)	
Radiation therapy	10 (13.2)	2 (8.3)	
Unknown	8 (10.5)	0 (0.0)	

HSCT indicates hematopoietic stem cell transplantation; IFN, interferon; IL-2, interleukin-2.

transplant; another was alive in MR at 6 months, with subsequent ongoing reductions in tumor mass; 3 were alive with SD at 19.1, 21.3, and 64.2 months; and 1 was alive with PD at 48.3 months (Table 4).

aGVHD developed in 15 patients, and all of those patients were treated with corticosteroids. Of these 15 patients, 7 patients had disease response (CR or PR); of the 9 patients who did not develop GVHD, only 1 showed disease response ($P = .19$).

Thirteen DLIs were performed in 8 patients. Two of those patients (20%) developed aGVHD after DLI. No disease responses were observed after DLI.

In the no-HSCT group, 12 patients were alive at last follow-up (Table 5), 5 with SD, 5 with PD, and 2 with unknown disease status. Of the 12 survivors, at least 5 had received targeted therapy after consultation, and 3 were alive without evidence of disease progression.

Survival

OS rates from the time of the consultation for the HSCT group and the no-HSCT subgroup (excluding the 31 patients with poor PS or brain metastases from the no-HSCT group) are shown in Figure 2. The median survival times were 15.2 months (range: 3.2-65.6 months) for the HSCT group and 18 months (range: 1.9-62.6 months) for the no-HSCT subgroup (excluding patients with poor PS or brain metastases) ($P = .92$). The median survival times from diagnosis were 42.8 months (range: 16-200 months) for the HSCT group and 30.4 months (range: 5.9-126 months) for the no-HSCT subgroup ($P = .44$). The median survival time from transplantation for the HSCT group was 8.4 months (range: 0.6-64.2 months). Seventeen patients in the HSCT group and 33 patients in the no-HSCT subgroup died during the study period. In the HSCT group, the median time from diagnosis to death was 35.6 months (range: 16.0-64.3 months). In no-HSCT subgroup, median time from diagnosis to death was 24.1 months (range: 5.9-124.5 months) ($P = .97$).

Prognostic Factors

We used both univariate and multivariate analyses to analyze possible prognostic factors. Excluded from the analyses were patients with poor PS or brain metastasis (n = 31), who were originally considered to have poor prognosis, and 5 other patients in the no-HSCT group because of unavailable laboratory data at the time of consultation. Findings from the analyses of factors possibly associated with OS time (from consultation) for the 63 remaining subjects are summarized in Table 6. In univariate analyses, Fuhrman's nuclear grade 4 ($P = .05$), high serum calcium level (corrected level >10 g/dL) ($P = .002$), low hemoglobin level (<13 g/dL for males or <11.5 g/dL for females) ($P = .02$), 3 or more number of sites of metastatic disease ($P = .02$), and <12 months from diagnosis to initial recurrence before consultation ($P = .04$) were identified as poor prognostic factors

Table 3. *Causes of Death after HSCT*

Causes	Number of Patients (%)	Days from HSCT Until Death
Progressive disease	8 (47)	Median 245 (range: 65-885)
Graft-versus-host disease	2 (12)	19 and 48
Pneumonia	3 (17)	77, 175, and 743
Acute respiratory distress syndrome	1 (6)	85
Thrombotic thrombocytopenic purpura	2 (12)	175 and 590
Acute myocardial infarction	1 (6)	76

Table 4. *Characteristics of Survivors in the Transplant Group*

Patient No.	Cell Source	Metastatic Sites at Consultation	Treatment before Consultation	Disease Status at Transplant	Sites of Grade II-IV Acute GVHD	No. of DLIs	Sites of Chronic GVHD	Overall Best Response	Treatment After Transplant	Disease Status at Last Follow-Up*
1	MSD PB	Remaining kidney, pancreas	Nephrectomy, IL-2, IFN	PD	Skin	0	Skin, mouth	SD	—	SD, 19.1 mo
2	MSD PB	Lung, retroperitoneal mass	Nephrectomy	PD	Skin, GI	0	—	CR	—	SD, 64.2 mo
3	MSD PB	Lung	Nephrectomy, IFN,IL-2, fluorouracil	PD	GI	0	Skin, mouth	CR	—	CR, 28.7 mo
4	MSD PB	Bone, lung	Nephrectomy, fluorouracil, IL-2, IFN; fluorouracil, gemcitabine; thalidomide, RT	SD	—	1	—	MR	TAE	PD, 48.3 mo
5	MSD PB	Retroperitoneal, liver	Nephrectomy, IFN, FUDR; thalidomide, IL2; capecitabine, gemcitabine	PD	Skin	0	Skin	SD	anti-VEGF elrotinib	SD, 21.3 mo
6	MSD PB	Lung, liver, pancreas	Nephrectomy, RT; capecitabine, gemcitabine	PD	—	0	—	MR	—	MR, 6.0 mo

GVHD indicates graft-versus-host disease; DLI, donor lymphocyte infusion; MSD, matched sibling donor; PB, peripheral blood; IL-2, interleukin-2; IFN, interferon; PD, progressive disease; SD, stable disease; GI, gastrointestinal; CR: complete remission, TAE, transcatheter arterial embolization; RT, radiation therapy; FUDR, floxuridine; VEGF, vascular endothelial growth factor; MR, minor response.

*Shown as time since transplant.

Table 5. *Characteristics of Survivors in the No-Transplant Group*

Patient No.	Metastatic Sites at Consultation	Treatments before Consultation	Treatments after Consultaion	Reason for Not Having Transplant	Disease Status at Last Follow-Up*
7	Lung, lymph node (mediastinal)	Nephrectomy, IFN	capecitabine, gemcitabine	Not interested	PD, 43.7 mo
8	Lungs, liver	Nephrectomy, heat shock vaccine, IL-2, IFN	thalidomide, sorafenib	No donor	SD, 77.7 mo
9	Lung, bone, liver, lymph node	Nephrectomy, IFN	IFN (continued), multiple chemo regimens (details unknown)	No donor	PD, 31.0 mo
10	Lung, bone	Nephrectomy, fluorouracil, gemcitabine, IFN	RT	Not interested	SD, 38.6 mo
11	Lung, liver	Nephrectomy, IFN	IL2 (no subsequent info available)	Not interested	NA, 22.2 mo
12	Lymph node (retroperitoneal, suplaclavicular)	Nephrectomy	ABT-510, anti-VEGF, erlotinib, paclitaxel, carboplatin	Not interested	SD, 20.9 mo
13	Lung, GI tract	Nephrectomy	IL-2, thalidmide, RT, erlotinib	No donor	PD, 60.2 mo
14	Lungs, bone, psoas muscle	Nephrectomy	IL2, sorafenib, surgery	No donor	PD, 64.4 mo
15	Bone, lymph node (mediastinal)	Nephrectomy	thalidomide, sorafenib, anti-VEGF, erlotinib, Imatinib	Not interested	SD, 33.0 mo
16	Lung, liver	Nephrectomy	IFN, capecitabine, gemcitabine	Not interested	SD, 47.5 mo
17	Lung, lymph node (mediastinal)	Nephrectomy	IL2 (no subsequent info available)	No donor	NA, 29.9 mo
18	Lung	Nephrectomy	IFN, capecitabine, gemcitabine, fluorouracil	Financial	PD, 22.4 mo

IFN indicates interferon; PD, progressive disease; SD, stable disease; RT, radiation therapy; IL2, interleukin-2; VEGF, vascular endothelial growth factor; NA, not available.
*Shown as time since transplant.

Figure 2. OS of patients who did undergo HSCT and those who did not (no-HSCT), excluding patients with poor PS or brain metastasis (BM), calculated from the time of the consultation. Median survival times: HSCT group, 15 months (range: 3.2-65.6 months); no-HSCT subgroup, 18 months (range: 19.0-62.6 months).

among all patients. Multivariate analyses identified 3 or more metastatic sites ($P = .005$) and low hemoglobin level ($P = .02$) as being poor prognostic factors (Table 6). Survival curves for patients in the HSCT group (n = 23) and the no-HSCT subgroup (n = 40, excluding patients with poor PS or brain metastasis or unavailable lab data) according to number of risk factors (number of metastatic sites ≥ 3 and low hemoglobin level) are shown in Figure 3. In the HSCT group, median survival time from the time of consultation for patients with 0 risk factors (n = 7) was 25 months; that for patients with 1 or more prognostic factors (n = 16) was 11 months ($P = .01$) (Figure 3A). In the no-HSCT subgroup (excluding patients with poor PS or brain metastasis or unavailable lab data), the median survival time from the consultation was 22 months for those with 0 prognostic factors (n = 21) and 9 months for those with 1 or more prognostic factors (n = 19) ($P = .03$) (Figure 3B).

DISCUSSION

We retrospectively identified prognostic factors associated with poor survival, not only for those who had HSCT but also for those who had not. In this study, we did not see a difference in OS between the HSCT and the no-HSCT group. Thus, previous concerns that HSCT would negatively affect long-term outcome of patients with metastatic RCC were not confirmed. This lack of difference in OS may have resulted from the somewhat high TRM rates, which are comparable to or slightly higher than those reported in previous studies [27-30,33-35]. These mortality rates may have offset any survival benefit produced by HSCT in this patient population. In

Table 6. *Prognostic Factors Associated with Overall Survival from the Time of Consultation*

Variables	Overall Survival *P* Values		Hazard Ratio	95% CI for HR
	Univariate	Multivariate		
Fuhrman's nuclear grade 4	.05			
High serum calcium	.002			
Low hemoglobin	.02	.02	2.29	1.16-4.52
Time between diagnosis and recurrence <12 months	.04	.06	1.95	0.96-3.94
Metastatic organ sites ≥3	.02	.005	3.19	1.42-7.16

CI indicates confidence interval; HR, hazard ratio.

addition, a longer interval between diagnosis and consultation and having had more previous treatments (relative to the no-HSCT group) may also have offset any survival benefit.

Our results indicate that patients with at least 1 of the prognostic factors identified in this study should not undergo HSCT. Our prognostic factors could be useful tools for identifying patients who are likely to have better versus worse prognosis after HSCT. Because our analyses were based on the time of first consultation for HSCT, our analysis is unlike other studies in which prognostic factors were sought for patients with similar disease status (eg, after nephrectomy, after cytokine therapy, or with cytokine-refractory disease) [37-40]. Our findings may be helpful for predicting prognosis in outpatient settings, where physicians ordinarily see and provide consultations for such patients whether they undergo HSCT or not.

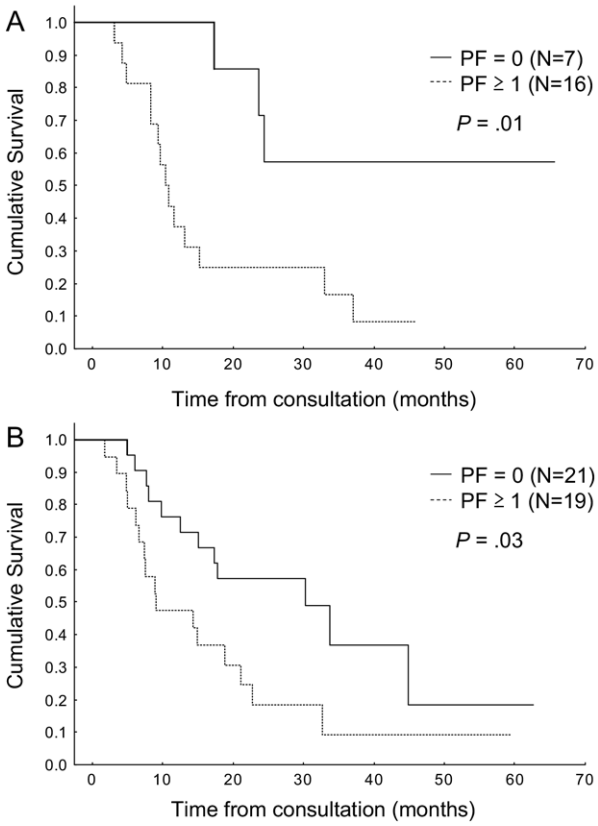

Figure 3. A, OS from consultation of patients who did undergo HSCT according to number of prognostic factors. Median survival times: 0 prognostic factors, 24.5 months (range: 17.4-65.6 months); 1 or more prognostic factors, 10.7 months (range: 3.2-46.0 months) (P = .01). PF, number of prognostic factors. B, OS from consultation of a subset of 40 patients who did not undergo HSCT (no-HSCT) (excluding 31 patients with poor PS or brain metastases and 5 patients for whom laboratory data were not available at consultation) according to number of prognostic factors. Median survival times: 0 prognostic factors, 22 months (range: 5.0-62.6 months); 1 or more prognostic factors, 9 months (range: 1.9-59.6 months) (P = .03). PF, number of prognostic factors.

When this study was reported, 3 other studies had been published regarding prognostic factors affecting OS for patients who received HSCT [41-43]. Two of those studies indicated that high PS, high lactate dehydrogenase (LDH) levels, and high C-reactive protein levels [41], or high PS and low hemoglobin levels [42], were associated with poor prognosis. The other study indicated that the existence of chronic GVHD (cGVHD), a history of DLI, <3 metastatic sites, and a Karnofsky score >70% were associated with good prognosis [43]. In our study, neither high PS nor high LDH level was associated with poor prognosis (we did not examine C-reactive protein), because we excluded patients with a PS scores of 2 or more. In fact, when patients with high PS were included in the analyses, both high PS (≥2) and high LDH level were significantly associated with poor prognosis in univariate analysis (P = 0.01 and 0.05) (data not shown). Aside from C-reactive protein levels, cGVHD, and DLI, all of these factors had already been reported as prognostic factors for no-HSCT patients with metastatic RCC [37,38,44-49], suggesting that these factors may affect the survival of patients who undergo HSCT as well as those who do not. In other words, the prognosis for patients undergoing HSCT depends on the original disease prognosis, and hence, HSCT should be considered before disease-related PS becomes poor. In our study, about 30% of patients were already ineligible for HSCT at the time of consultation because of having high PS scores or brain metastases. This means that delays in seeking consultation may have rendered some of these patients ineligible for a transplant. Early referral to a transplant service is recommended for patients who may be eligible to undergo HSCT before

their PS deteriorates to the point of rendering them ineligible.

On the other hand, our findings also showed that patient refusal was another major reason for not undergoing a transplant. In our sample, significantly fewer patients in the no-HSCT group had been given IL-2 therapy, and patients in the no-HSCT group had had fewer numbers of treatment cycles than was true in the HSCT group. Logically, one might assume that patients who had not yet been given cytokine therapy or several cycles of chemotherapy may have elected to receive 1 or both of those rather than a transplant, possibly because the cytokine therapy and chemotherapy were perceived as being safer. This indicates that early referral to a transplant service does not necessarily encourage patients to choose HSCT. Clearly, close cooperation between oncologists, stem cell transplantation physicians, and patients will be needed to avoid missing the best time for HSCT.

Recent results of a Cancer and Leukemia Group B (CALGB)—Intergroup phase II study of allogeneic HSCT for metastatic RCC [50] showed that no objective responses were observed in the 22 patients enrolled despite the presence of both aGVHD and cGVHD. On the other hand, a recent European study showed that the overall response rate (CR + PR) in a given allogeneic HSCT for metastatic RCC was 29% [43], a finding similar to ours. One possible reason for this discrepancy is that more of the patients in the CALGB study may have had poor prognostic factors; for example, 45% of the patients in that study had 3 or more metastatic sites, whereas only 18% of the patients in our study did. The report of the European study did not include information on number of metastatic disease sites.

Recent studies of the efficacy of targeted therapy for metastatic RCC have shown response rates of 2% to 40% [23]. In our study, relatively few of the patients received targeted therapy, probably because few clinical trials of targeted therapy had been undertaken during our study period. In our HSCT group, 16 (70%) of the 23 patients got a transplant during or before 2002, and the other 7 patients got a transplant after 2002. Of the 8 patients who eventually died after transplant of disease progression, 5 died in 2001 or 2002, and only 3 died during or after 2003 (data not shown); it is possible that patients who underwent transplantation early during the study period would have been ineligible to participate in clinical trials of tyrosine-kinase inhibitors. The use of targeted therapy could be expected to increase as its efficacy becomes better established. Given the importance of low TRM rates during targeted therapy, allogeneic HSCT could perhaps best be applied, on a trial basis, to patients with disease refractory to targeted therapy. Furthermore, the effectiveness of targeted therapy for progressive disease after HSCT remains unclear. This speculation should be validated in the context of clinical trials.

Our results must be interpreted cautiously; the retrospective nature of our study may have introduced various selection biases, which can render the results misleading. Nonetheless, it is clear that HSCT is an active treatment for some patients with no poor prognostic factors. In this study, of the 6 survivors of HSCT, 1 achieved CR, and this patient was in still CR when this paper was written; another 4 patients are under observation without additional treatment. These facts may indicate that these patients benefitted from HSCT. Over the past 5 years, TRM rates associated with HSCT have dropped to <10% through improvements in transplant technology and experience. However, future efforts are needed to establish means of separating GVT effects from GVHD. Ideal treatment approaches, especially for targeted-therapy-resistant RCC, need to be established. The potential efficacy of HSCT for metastatic RCC that does not respond to targeted therapies (eg, sorafenib, sutinib) should be tested in clinical trials to conclusively determine whether transplantation is a treatment option for this deadly disease.

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